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(54) Title: SOLID DISPERSION COMPOSITIONS OF TEBUFELONE**(57) Abstract**

The subject invention relates to compositions in dosage form comprising a solid dispersion which is a solidified melt mixture consisting essentially of the following components: (a) from about 15 % to about 75 % of tebufelone; (b) from about 25 % to about 65 % of a poloxamer surfactant having a melting point of about 40 °C or greater, the poloxamer surfactant consisting essentially of a block copolymer having three polymer blocks, a middle block of poly(oxypropylene) with a molecular weight of from about 1450 daltons to about 6000 daltons, and end blocks of poly(oxyethylene), the end blocks being from about 50 % to about 90 % of the copolymer; and (c) from 0 % to about 60 % of other components, wherein the other components are miscible with a melt mixture of components (a) and (b).

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SOLID DISPERSION COMPOSITIONS OF TEBUFELONE

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TECHNICAL FIELD

10 The subject invention involves novel pharmaceutical compositions containing tebufelone, a di-tert-butylphenol anti-inflammatory compound. More particularly, it involves such compositions dosed perorally which provide good bioavailability of the compound.

BACKGROUND OF THE INVENTION

15 Certain substituted di-tert-butylphenol derivatives are known to be effective as anti-inflammatory, analgesic and/or antipyretic agents. Of particular interest regarding the subject invention is tebufelone, 1-3,5-bis(1,1-dimethylethyl)-4-hydroxy-phenyl-5-hexyn-1-one disclosed in U.S. Patent No. 4,708,966 issued to Loomans, Matthews & Miller on November 24, 1987. (The compound is termed 4-(5'-hexynoyl)-2,6-di-tert-butylphenol therein.) Related compounds are disclosed in U.S. Patent No. 4,846,303 issued to Loomans, Matthews & Miller on July 11, 1989 and U.S. Patent No. 4,849,428 issued to Dobson, Loomans, Matthews & Miller on July 18, 1989. Certain compositions of tebufelone are disclosed in European Patent Application No. 0,431,659 of Kelm & Bruns published June 12, 1991.

20 It is an object of the subject invention to provide solid dispersion pharmaceutical compositions for peroral administration of tebufelone which provide good bioavailability of the compound.

SUMMARY OF THE INVENTION

25 The subject invention relates to compositions in dosage form comprising a solid dispersion which is a solidified melt mixture consisting essentially of the following components:

- (a) from about 15% to about 75% of tebufelone;
- (b) from about 25% to about 65% of a poloxamer surfactant having a melting point of about 40°C or greater, the poloxamer surfactant consisting essentially of a block copolymer having three polymer blocks, a middle block of poly(oxypropylene) with a molecular weight of from

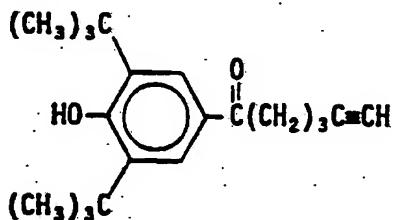
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about 1450 daltons to about 6000 daltons, and end blocks of poly(oxyethylene), the end blocks being from about 50% to about 90% of the copolymer; and

5 (c) from 0% to about 60% of other components, wherein the other components are miscible with a melt mixture of components (a) and (b).

DETAILED DESCRIPTION OF THE INVENTION

The drug active of interest regarding the subject invention is 1-3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl-5-hexyn-1-one 10 having the chemical structure:



15 which is referred to herein as tebufelone. A method of synthesizing tebufelone is disclosed in aforementioned U.S. Patent No. 4,708,966, which is hereby incorporated herein by reference.

20 The subject invention involves pharmaceutical compositions of tebufelone intended for peroral administration to humans and lower animals. The subject compositions comprise solid dispersions which comprise tebufelone and certain poloxamer surfactants. As used herein, "solid dispersion" means a material 25 which is solid at specified temperatures, and which has been produced by blending melted tebufelone and poloxamer (and other components, if present), whereby a homogeneous melt mixture results, and cooling the resulting melt mixture so that it forms a solid with the components substantially uniformly dispersed 30 therein.

The solid dispersions of the subject invention comprise from about 15% to about 75% tebufelone, preferably from about 25% to about 60% tebufelone; more preferably from about 35% to about 50% tebufelone. The melting point of tebufelone is about 70°C.

35 It has been found that tebufelone is essentially water-insoluble (solubility less than 1 $\mu\text{g}/\text{ml}$) and very lipophilic. The therapeutic dose of tebufelone is from about 10 mg to about

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600 mg per day in humans. It has been found that the absorption of tebufelone from the gastrointestinal tract is quite low when the active is dosed in conventional dosage forms, where solid particles of substantially pure tebufelone are mixed with other 5 solid excipients and filled into hard gelatin capsules or compressed into tablets. It has been found that good absorption of tebufelone from the gastrointestinal tract occurs only when the drug active is orally administered in pharmaceutical compositions which provide rapid solubilization of the drug active in 10 the gastrointestinal fluids. As used herein, being solubilized means that the drug active exists in an aqueous medium in a form that is freely diffusible. A free diffusible form is one that is capable of transversing the unstirred boundary layer present along the absorbing membrane of the gastrointestinal tract. Such 15 freely diffusible forms include a pure aqueous solution of the drug active, an aqueous micellar solution of the drug active (drug molecules dissolved in surfactant micelles), and/or an emulsion of the drug active (liquid droplets containing drug actives surrounded by a surfactant layer dispersed in an aqueous 20 medium).

It has been found that rapid solubilization of tebufelone in gastrointestinal fluids can be achieved from the compositions of the subject invention which comprise solid dispersions comprising tebufelone with certain poloxamer surfactants. The subject solid 25 dispersions have melting points of about 40°C or higher, preferably of from about 45°C to about 100°C; more preferably from about 50°C to about 80°C.

The poloxamer surfactants useful in the compositions of the subject invention have melting points of about 40°C or higher, 30 yet have been found to provide the necessary solubilization of tebufelone. These poloxamer surfactants are block copolymers having three polymer blocks. The middle block of the copolymer is poly(oxypropylene) having a molecular weight of from about 1450 daltons to about 6000 daltons, preferably from about 1600 daltons to about 5000 daltons, more preferably from about 35 1750 daltons to about 4000 daltons. The end polymer blocks are poly(oxyethylene). The two poly(oxyethylene) end blocks together

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comprise at least about 50% of the weight of the block copolymer, preferably from about 50% to about 90%, more preferably from about 70% to about 80%. The average molecular weight of the block copolymer is from about 3000 to about 50,000, more preferably from about 4500 to about 25,000, most preferably from about 6500 to about 15,000. The melting point of the block copolymer is preferably from about 40°C to about 80°C, more preferably from about 45°C to about 60°C, most preferably from about 50°C to about 60°C. Mixtures of suitable poloxamer surfactants can be used in the solid dispersions of the subject invention. The subject solid dispersions comprise from about 25% to about 65% of poloxamer surfactant, preferably from about 35% to about 50%.

Preferred examples of poloxamer surfactants useful in the solid dispersions of the subject invention include the following which are commercially available from BASF Wyandotte Corp., Parsippany, NJ: Poloxamer 188 (Pluronic F68®), which is 80% poly(oxyethylene) and has a molecular weight of 8350 daltons and a melting point of 52°C; Poloxamer 217 (Pluronic F77®), which is 70% poly(oxyethylene) and has a molecular weight of 6600 daltons and a melting point of 48°C; Poloxamer 235 (Pluronic P85®), which is 50% poly(oxyethylene) and has a molecular weight of 4600 daltons and a melting point of 40°C; Poloxamer 237 (Pluronic F87®), which is 70% poly(oxyethylene) and has a molecular weight of 7700 daltons and a melting point of 49°C; Poloxamer 238 (Pluronic F88®), which is 80% poly(oxyethylene) and has a molecular weight of 10800 daltons and a melting point of 54°C; Poloxamer 288 (Pluronic F98®), which is 80% poly(oxyethylene) and has a molecular weight of 13500 daltons and a melting point of 55°C; Poloxamer 235 (Pluronic P105®), which is 50% poly(oxyethylene) and has a molecular weight of 6500 daltons and a melting point of 42°C; Poloxamer 338 (Pluronic F108®), which is 80% poly(oxyethylene) and has a molecular weight of 14000 daltons and a melting point of 57°C; and Poloxamer 407 (Pluronic F127®), which is 70% poly(oxyethylene) and has a molecular weight of 12500 daltons and a melting point of 56°F.

Solid dispersions of the subject invention may also include other components which are miscible with the tebufelone/poloxamer

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surfactant melt mixture. As used herein, being "miscible" with the tebufelone/poloxamer surfactant melt mixture means that the other components can be melted and mixed with the tebufelone/poloxamer surfactant melt mixture to form a homogeneous melt mixture, or the other components dissolve in the tebufelone/poloxamer melt mixture to form a homogeneous mixture. Other components of the solid dispersions of the subject invention are limited to those that result in the solid dispersion having a melting point of about 40°C or higher, as provided hereinabove.

Examples of other components which are suitable for incorporation in the solid dispersions of the subject invention include other surfactants, and certain low molecular weight water-soluble materials. Preferred other surfactants include polysorbates (polyoxyethylene sorbitan fatty acid esters), polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, and polyoxyethylene stearates. Such other surfactants preferably have an HLB (hydropholic-lipophilic balance) greater than about 14. Polysorbates are included in the solid dispersions of the subject invention at levels of from 0% to about 60%, preferably from about 20% to about 40%; other surfactants are included at levels of from 0% to about 20%.

Preferred polysorbates useful in the solid dispersions of the subject invention include the following which are available commercially from ICI Americas, Inc., Stratford, CT: Polysorbate 20 (Tween 20[®]) having an HLB of 16.7, Polysorbate 40 (Tween 40[®]) having an HLB of 15.6, Polysorbate 60 (Tween 60[®]) having an HLB of 14.9, and Polysorbate 80 (Tween 80[®]) having an HLB of 15.0.

Preferred polyoxyethylene alkyl ethers include those sold under the trade name Brij[®] available commercially from ICI Americas, Inc. Preferred polyoxyethylene castor oil derivatives include those sold under the trade name Cremophor[®], e.g., RH 40 and RH 60, available commercially from BASF Wyandotte Corp., Parsippany, NJ. Preferred polyoxyethylene stearates include those sold under the trade name Emerest[®] available commercially from Emery Industries, Inc., Linden, NJ.

Another preferred additional component of the solid dispersions of the subject invention is a polyethylene glycol (PEG).

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PEGs are condensation polymers of ethylene oxide. Preferred PEGs are those with nominal molecular weights in excess of about 1500 daltons, preferably from about 2000 to about 20,000 daltons, more preferably from about 3000 daltons to about 8000 daltons.

5 Examples include PEGs available commercially from Union Carbide Corp., Jacksonville, FL under the trade name Carbowax®. PEGs are incorporated in the subject solid dispersions at levels of from 0% to about 60%, preferably from about 20% to about 40%.

Preferred solid dispersions of the subject invention consist 10 essentially of tebufelone and poloxamer; tebufelone, poloxamer and polysorbate; tebufelone, poloxamer and PEG; or tebufelone, poloxamer, polysorbate and PEG; the quantity of each component being that disclosed hereinabove.

Other excipients which can be incorporated in the solid 15 dispersions of the subject invention include urea (preferably from 0% to about 20%) and dextrose monohydrate (preferably from 0% to about 20%).

Solid dispersions of the subject invention are preferably 20 made by melting the tebufelone and the poloxamer surfactant together, with mixing, to form a homogeneous melt mixture. Solid dispersions of the subject invention are made by cooling this binary melt mixture and allowing it to solidify. Other solid dispersions of the subject development are made by adding other components to the binary melt mixture, mixing to form a homogeneous melt mixture, and cooling the resulting melt mixture to 25 solidify it.

Preferred dosage form compositions of the subject invention are made from the above solid dispersions. Preferred solid dispersions of the subject invention can be formed into flowable 30 particles by suitable means. The particles are then formulated into conventional dosage forms, such as tablets and capsules. Suitable means of producing the particles include oscillating screen size reduction of solidified melt mixtures and prilling of the melt.

35 An especially preferred dosage form consists of a hard gelatin capsule into which the homogeneous melt mixture is filled and allowed to solidify in situ. Another dosage form composition

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is made by filling the melt mixture into soft, elastic gelatin capsules. Another dosage form is made by forming molded tablets, e.g., by filling the melt mixture into tablet molds, or shaping partially solidified melt mixture into tablet shapes.

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EXAMPLES

The following are non-limiting examples of compositions of the subject invention.

Example 1

10	Tebufelone	50%
	Poloxamer 407	50%

The two components are melted at 75°C to form a homogeneous liquid which is allowed to solidify at ambient temperature. The resulting solid is milled using an oscillating screen to particle size of about 230 to 860 µm. The particles are filled into hard gelatin capsules using conventional capsule filling equipment.

Example 2

20	Tebufelone	40%
	Poloxamer 238	40%
	Polysorbate 80	20%

Example 3

25	Tebufelone	20%
	Poloxamer 338	40%
	Polysorbate 80	40%

Tebufelone and Poloxamer 338 are melted at 85°C to form a homogeneous liquid to which Polysorbate 80 is added with mixing. The resulting melt mixture is filled into hard gelatin capsules using modified capsule filling equipment and allowed to solidify.

Example 4

35 Tebufelone 30%
Poloxamer 338 30%
PEG (MW=20,000) 40%

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The three components are melted at 85°C and blended to form a homogeneous liquid which is filled into standard suppository molds and allowed to solidify into molded tablets.

5 While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

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1. A composition in dosage form comprising a solid dispersion which is a solidified melt mixture consisting essentially of the following components:

5 (a) from 15% to 75%, preferably from 35% to 60%, of
tebufelone;

10 (b) from 25% to 65%, preferably from 35% to 50%, of a poloxamer surfactant having a melting point of 40°C or greater, preferably 50°C to 80°C, the poloxamer surfactant being a block copolymer having three polymer blocks, a middle block of poly(oxypropylene) with a molecular weight of from 1450 to 6000 daltons, and end blocks of poly(oxyethylene), the end blocks being from 50% to 90%, preferably from 60% to 80%, by weight of the copolymer; and

15 (c) from 0% to 60%, preferably from 20% to 40%, of other components, wherein the other components are miscible with a melt mixture of components (a) and (b).

2. A composition of Claim 1 wherein the other components
comprise polyethylene glycol having a molecular weight of 1500 or
greater, preferably a molecular weight of from 3000 to 20,000.

3. The composition of Claim 1 or 2 wherein the other components comprise a surfactant, preferably a polysorbate, having an HLB of 14 or greater.

4. The composition of any of Claims 1, 2 and 3 wherein the poloxamer surfactant has a molecular weight of from 6500 to 15,000.

30 5. The composition of any of Claims 1, 2, 3 and 4 wherein the poloxamer surfactant is selected from Poloxamer 188, Poloxamer 217, Poloxamer 235, Poloxamer 237, Poloxamer 238, Poloxamer 288, Poloxamer 235, Poloxamer 338, and Poloxamer 407.

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6. The composition of any of Claims 1, 2, 3, 4 and 5 wherein the polysorbate is selected from Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80.

5 7. The composition of Claim 1, wherein the composition comprises 20% tebufelone, 40% Poloxamer 338, and 40% Polysorbate 80.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 93/04050

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 A61K31/12; A61K9/14

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	A61K
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸	

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 431 659 (PROCTER & GAMBLE) 12 June 1991 cited in the application see the whole document ----	1-7
A	EP,A,0 251 408 (PROCTER & GAMBLE) 7 January 1988 cited in the application see the whole document ----	1-7
A	EP,A,0 313 303 (PROCTER & GAMBLE) 26 April 1989 see the whole document -----	1-7

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

30 AUGUST 1993

Date of Mailing of this International Search Report

09.09.93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

SCARPONI U.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 9304050
SA 74429

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 30/08/93

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